mediators, such as histamine, leukotrienes, and prostaglandin D_2, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

Pharmacokinetics: ***ADVAIR DISKUS:*** Following administration of ADVAIR DISKUS to healthy subjects, peak plasma concentrations of fluticasone propionate were achieved in 1 to 2 hours and those of salmeterol were achieved in about 5 minutes.

In a single-dose crossover study, a higher than recommended dose of ADVAIR DISKUS was administered to 14 healthy subjects. Two inhalations of the following treatments were administered: ADVAIR DISKUS 500/ 50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, and fluticasone propionate powder 500 mcg alone. Mean peak plasma concentrations of fluticasone propionate averaged 107, 94, and 120 pg/ mL, respectively, and of salmeterol averaged 200 and 150 pg/ mL, respectively, indicating no significant changes in systemic exposures of fluticasone propionate and salmeterol.

In a repeat-dose study, the highest recommended dose of ADVAIR DISKUS was administered to 45 asthmatic patients. One inhalation twice daily of the following treatments was administered: ADVAIR DISKUS 500/ 50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, or fluticasone propionate powder 500 mcg alone. Mean peak steady-state plasma concentrations of fluticasone propionate averaged 57, 73, and 70 pg/ mL, respectively, indicating no significant changes in systemic exposure of fluticasone propionate. No plasma concentrations of salmeterol were measured in this repeat-dose study.

No significant changes in excretion of fluticasone propionate or salmeterol were observed. The terminal half-life of fluticasone propionate averaged 5.33 to 7.65 hours when ADVAIR DISKUS was administered, which is similar to that reported when fluticasone propionate was given concurrently with salmeterol or when fluticasone propionate was given alone (average, 5.30 to 6.91 hours). No terminal half-life of salmeterol was reported upon administration of ADVAIR DISKUS or salmeterol given concurrently with fluticasone propionate.

Special Populations: Formal pharmacokinetic studies using ADVAIR DISKUS were not conducted to examine gender differences or in special populations, such as elderly patients or patients with hepatic or renal impairment.

Drug-Drug Interactions: In the repeat-and single-dose studies, there was no evidence of significant drug interaction in systemic exposure between fluticasone propionate and salmeterol when given as ADVAIR DISKUS.

Fluticasone Propionate: Absorption: Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed. The systemic bioavailability of fluticasone propionate from the DISKUS device in healthy volunteers averages 18%.

Peak steady-state fluticasone propionate plasma concentrations in adult patients (n = 11) ranged from undetectable to 266 pg/ mL after a 500-mcg twice-daily dose of fluticasone propionate inhalation powder using the DISKUS device. The mean fluticasone propionate plasma concentration was 110 pg/ mL.

Distribution: Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/ kg.

The percentage of fluticasone propionate bound to human plasma proteins averages 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

Metabolism: The total clearance of fluticasone propionate is high (average, 1093 mL/ min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed

through the cytochrome P450 3A4 pathway. This metabolite had less affinity (approximately 1/2000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Elimination: Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Hepatic Impairment: Since fluticasone propionate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease should be closely monitored.

Gender: Full pharmacokinetic profiles were obtained from 9 female and 16 male patients given fluticasone propionate inhalation powder 500 mcg twice daily using the DISKUS. No overall differences in fluticasone propionate pharmacokinetics were observed.

Special Populations: Formal pharmacokinetic studies using fluticasone propionate were not carried out in other special populations.

Drug-Drug Interactions: In a multiple-dose drug interaction study, coadministration of fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics. In another drug interaction study, coadministration of fluticasone propionate (1000 mcg) and ketoconazole (200 mg once daily) resulted in increased fluticasone propionate concentrations and reduced plasma cortisol area under the plasma concentration versus time curve (AUC), but had no effect on urinary excretion of cortisol. Since fluticasone propionate is a substrate of cytochrome P450 3A4, caution should be exercised when cytochrome P450 3A4 inhibitors (e. g., ritonavir, ketoconazole) are coadministered with fluticasone propionate as this could result in increased plasma concentrations of fluticasone propionate.

Salmeterol Xinafoate: Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and eliminated independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

Absorption: Because of the small therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7 asthmatic patients; plasma concentrations were very low, with mean peak concentrations of 167 pg/ mL at 20 minutes and no accumulation with repeated doses.

Distribution: Binding of salmeterol to human plasma proteins averages 96% in vitro over the concentration range of 8 to 7722 ng of salmeterol base per milliliter, much higher concentrations than those achieved following therapeutic doses of salmeterol.

Metabolism: Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominantly in the feces. No significant amount of unchanged salmeterol base was detected in either urine or feces.

Elimination: In 2 healthy subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination half-life was about 5.5 hours (1 volunteer only). The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (> 99%) and has a long elimination half-life of 11 days.

Special Populations: Formal pharmacokinetic studies of salmeterol base have not been conducted in special populations. Since salmeterol is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

Pharmacodynamics: ***ADVAIR DISKUS:*** Since systemic pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher doses were used to produce measurable effects. Four studies were conducted in healthy subjects: (1) a single-dose crossover study using 2 inhalations of ADVAIR DISKUS 500/ 50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, or fluticasone propionate powder 500 mcg given alone, (2) a

the double-foil strip within the device contains 100, 250, or 500 mcg of microfine fluticasone propionate and 72.5 mcg of microfine salmeterol xinafoate salt, equivalent to 50 mcg of salmeterol base, in 12.5 mg of formulation containing lactose. Each blister contains 1 complete dose of both medications. After a blister containing medication is opened by activating the device, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized in vitro test conditions, ADVAIR DISKUS delivers 93, 233, and 465 mcg of fluticasone propionate and 45 mcg of salmeterol base per blister from ADVAIR DISKUS 100/ 50, 250/ 50, and 500/ 50, respectively, when tested at a flow rate of 60 L/ min for 2 seconds. In adult patients (n = 9) with obstructive lung disease and severely compromised lung function (mean forced expiratory volume in 1 second [FEV_1] 20% to 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS® device was 80.0 L/min (range, 46.1 to 115.3 L/ min).

Inhalation profiles for adolescent (n = 13, aged 12 to 17 years) and adult (n = 17, aged 18 to 50 years) patients with asthma inhaling maximally through the DISKUS device show mean PIF of 122.2 L/ min (range, 81.6 to 152.1 L/ min).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

CLINICAL PHARMACOLOGY:

Mechanism of Action: ***ADVAIR DISKUS:*** ADVAIR DISKUS is designed to produce a greater improvement in pulmonary function and symptom control than either fluticasone propionate or salmeterol used alone at their recommended dosages. Since ADVAIR DISKUS contains both fluticasone propionate and salmeterol, the mechanisms of action described below for the individual components apply to ADVAIR DISKUS. These drugs represent 2 classes of medications (a synthetic corticosteroid and a long-acting beta-adrenergic receptor agonist) that have different effects on clinical, physiological, and inflammatory indices of asthma.

Fluticasone Propionate: Fluticasone propionate is a synthetic, trifluorinated corticosteroid with potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results.

The precise mechanisms of fluticasone propionate action in asthma are unknown. Inflammation is recognized as an important component in the pathogenesis of asthma. Corticosteroids have been shown to inhibit multiple cell types (e. g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediator production or secretion (e. g., histamine, eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Salmeterol Xinafoate: Salmeterol is a long-acting beta-adrenergic agonist. In vitro studies and in vivo pharmacologic studies demonstrate that salmeterol is selective for $beta_2$-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on $beta_1$-and $beta_2$-adrenoceptors. In vitro studies show salmeterol to be at least 50 times more selective for $beta_2$-adrenoceptors than albuterol. Although $beta_2$-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta1-adrenoceptors are the predominant receptors in the heart, there are also $beta_2$-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of beta2-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell